REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at (858) 720-5133.

Telephonic interview of June 11, 2008

Applicants thank the Examiner for the very helpful and courteous telephonic interview on June 11, 2008, where the cited art in light of the instant invention was discussed, and allowable subject matter was discussed.

Status of the Claims

Pending claims

Claims 1 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127, 129 and 130 are currently pending.

Outstanding Rejections

Claims 1 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127, 129 and 130, are objected to. Claims 25, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Queen et al. USPN 5,693,762. Claims 25, 29, 31, 33, 34, 36 and 37, and 71 to 73 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kolbinger et al., Protein Engineering 6(8):971-980

Applicants respectfully traverse all outstanding objections and rejections of the claims.

Support for Claim Amendments

Support for the amended and new claims can be found throughout the application for the skilled artisan. For example, support for claims encompassing methods comprising modifying less than all, i.e., at least one but not all, amino acid positions in a non-human antibody framework regions (FR) can be found, inter alia, in the paragraph spanning pages 43 and 44, and on the first and second full paragraphs of page 44 (lines 8 to 24), which are paragraphs [0143] to [0145], respectively, of this application's publication U.S. Pat App Pub. No. 20040229310 ("the '310

publication"). See also the paragraph of lines 1 to 9, page 42, of the specification (paragraph [0125] of the '310 publication) describing alternative embodiments comprising modification of less than all, i.e., at least one but not all, amino acid positions in a non-human antibody FR. Support for claims encompassing methods comprising deleting specifically identified amino acid residues can be found, inter alia, on page 47, lines 19 to 26 (paragraph [0162] of the '310 publication). Support for claims encompassing methods of expressing antibodies in various types of cells, e.g., prokaryotic or eukaryotic cells, or filamentous fungi, yeast cells, insect cells, mammalian cells, bacterial cells, and the like, can be found, inter alia, on from line 10, page 51 to line 26, page 52 (paragraphs [0177] to [0180] of the '310 publication).

Accordingly, Applicants submit that no new matter is introduced by the present amendments.

Objections

Claims 1 to 25, 28 to 34, 36 to 61, 63 to 74, 96 to 114, 116 to 127, 129 and 130, are objected to for the reasons set forth in detail in paragraph 4, page 2, of the OA. The instant amendment addresses this issue.

Issues under 35 U.S.C § 102

Queen et al. USPN 5,693,762

Claims 25, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Queen et al. USPN 5,693,762, issued December 2, 1997, filed June 7, 1995 (hereinafter "Queen"), for reasons set forth in paragraph 9, page 3, of the OA.

As clarified by the instant amendment, Queen does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, which comprises:

aligning a hypervariable region (HVR1) and/or a hypervariable region 2 (HVR2) of a variable domain of non-human antibody or antigen binding fragment to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences;

selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

identifying at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human antibody or antigen binding fragment;

modifying one amino acid at the corresponding position of the non-human variable domain of the antibody or antigen binding fragment to be the same as the different human amino acid residue identified in (c) to form a modified FR region in the non-human variable domain of the antibody or antigen binding fragment.

Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

In contrast, as discussed in the telephonic interview, Queen compares Ab variable regions to be modified with human Ab variable region consensus sequences. Thus, in the method of Queen, FR sequences are involved in determining which human variable region consensus sequences are selected for use in the method. See, e.g., column 13, lines 4 to 10, and lines 47 to 49, of Queen.

See also claim 14, step (1) of Queen, which is directed to a method of producing a humanized immunoglobulin, comprising the step of (1) comparing the sequence of a donor immunoglobulin heavy chain variable region against a collection of sequences of human heavy chain variable regions.

The claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

Kolbinger et al.

Claims 25, 29, 31, 33, 34, 36 and 37, and 71 to 73 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kolbinger et al., Protein Engineering 6(8):971-980 (hereinafter "Kolbinger"), for reasons set forth in paragraph 10, page 4, of the OA.

As clarified by the instant amendment, Kolbinger does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Kolbinger, like Queen, compares variable regions to be modified with human variable region consensus sequences. See for example page 975, lines 1 to 8 of the first paragraph of the section "Design of the reshaped human C21 variable region", of Kolbinger, and lines 12 to 14 of the Materials and Methods section "Molecular modeling of the mouse C21 variable regions", of Kolbinger.

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

Bendig et al. USPN 5,558,864

Claims 25 and 29 to 31, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bendig et al. USPN 5,558,864, issued September 24, 1996, filed March 4, 1992 (hereinafter "Bendig"), for reasons set forth in paragraph 11, page 4, of the OA.

As clarified by the instant amendment, Bendig does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Bendig, like Kolbinger and Queen, compares variable regions to be modified with human variable region consensus sequences. In fact, in one aspect Bendig takes exactly the opposite

approach from that of this invention by comparing only FR sequences of mouse Ab (the Ab to be humanized) and human FR consensus sequences; see e.g., column 16, lines 26 to 36, of Bendig.

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

Baca et al. USPN 6,884,879

Claims 25, 28, 29, 31, 33, 34, 36 and 37, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Baca et al. USPN 6,884,879, issued April 26, 2005, filed August 06, 1997 (hereinafter "Baca, USPN 6,884,879"), for reasons set forth in paragraph 12, pages 5 to 6, of the OA.

As clarified by the instant amendment, Baca, USPN 6,884,879, does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Baca, USPN 6,884,879, like Bendig, Kolbinger and Queen, compares variable regions to be modified with human variable region consensus sequences. For example, see column 14, lines 40 to 67; and column 15, lines 30 to 43, of Baca, teaching alternative means to choose which FR amino acid residues to use – noting that Baca, USPN 6,884,879, always uses FR sequences in its comparisons.

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

Baca et al. WO 98/45331

Claims 25 to 31, 33, 34, 36 and 37, and 71 to 73, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Baca et al. WO 98/45331, published October 15, 1998, filed internationally April 03, 1998, and sharing a priority document filed August 06, 1997, with Baca, USPN 6,884,879 (hereinafter "Baca, WO 98/45331"), as evidenced by Queen, for reasons set forth in paragraph 13, page 6, of the OA.

As clarified by the instant amendment, Baca, WO 98/45331, does not teach any method for producing a non-human, recombinant antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Baca, WO 98/45331, prepares "humanized" antibodies by, e.g., inserting mouse CDRs (the part of the Ab that binds antigen) into a human antibody (swapping human CDR with mouse CDR), then randomly mutagenizes framework region residues, and chooses which random FR change results in the best binding antibody by routine antigen screening (Ag binding) methods (see, e.g., Example 2, pages 61 to 63. Interestingly, Baca, WO 98/45331, emphasizes the superiority of its "random" FR residue generating method by noting that the Ab designer is not limited to use of only human or murine amino acid sequences (see, e.g., page 62, lines 4 to 6).

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully aver that the Examiner can properly withdraw the objections to the claims and the rejections of the pending claims under 35 U.S.C. §102(b). In view of the above, all claims pending in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 146392004900. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has review the instant response and amendment, please telephone the undersigned at (858) 720-5133.

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Respectfully submitted,

By /Gregory P . Einhorn/
Gregory P. Einhorn
Registration No.: 38,440
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-5133 direct line
general office 858 720 5100
fax direct 858 523 5933
fax office 858 720 5125

email geinhorn@mofo.com